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Original Article

Clinical Manifestations and Outcomes of Cardiac Tumours in Children

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Abstract Cardiac tumours occur rarely in children. We report on the clinical features, echocardiogram and electrocardiographic findings, treatment, and outcomes of primary cardiac tumours in 27 children treated between 2009 and 2017 in our single centre. The most common tumour was rhabdomyoma with tuberous sclerosis in 15 children; two malignant tumours-an angiosarcoma and rhabdomyosarcoma-were also found. Seven patients were haemodynamically unstable: five underwent cardiac surgery, one was managed with everolimus for arrhythmia, and one died of heart failure 1 day after birth despite full medical support. We discuss the various treatment options for haemodynamically unstable paediatric patients with a cardiac tumour.

Key words Cardiac surgery; Cardiac tumour; Rhabdomyoma

Introduction

Cardiac tumours are rare in children.[1,2] The prevalence of primary cardiac tumours in autopsy studies of the paediatric population is 0.0017-0.28%, and the incidence is 0.14% during fetal life.[3] The most frequently encountered primary tumours are rhabdomyomas, which are associated with tuberous sclerosis, followed by fibromas, which account for 80% of primary cardiac tumours.[3,4] In children, cardiac tumours present at different ages and as different clinical entities according to the histological type, size, and location. Most cardiac tumours have benign features but may also present with heart failure, haemodynamically unstable arrhythmia, and sudden death. We have treated paediatric patients with various cardiac tumours, which ranged from benign to malignant and which needed cardiac surgery or medication. Here we present the results of our evaluation of the clinical presentation, treatment, and outcomes in paediatric patients with a cardiac tumour treated in our centre.

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Methods

We performed a retrospective observational study of patients diagnosed with cardiac tumours at Pusan National University Children's Hospital, Pusan, Korea, from January 2009 to August 2017. We identified 33 patients who had been diagnosed with a primary cardiac tumour during this 9-year period and reviewed their medical records. Six of the 33 patients were excluded because of loss to follow-up after the first diagnosis. We analysed the clinical presentation, treatment, outcome, and electrocardiographic findings for the remaining 27 patients, and we focused on seven haemodynamically unstable patients. We could not analyse the data according to tumour histological type

because this was confirmed in only five patients who had undergone surgical excision. Of these five patients, one had a huge fibroma, two had a malignant sarcoma, and two had confirmed rhabdomyomas. Thirteen other patients had benign rhabdomyomas associated with tuberous sclerosis, and nine had a benign course without tuberous sclerosis, except for one who died on postnatal day 1. The indication for the surgical removal of a cardiac tumour was an obstructive or haemodynamically unstable mass.

The study was approved by the Pusan National University Yangsan Hospital Institutional Review Board. All data were analysed using SPSS for Windows, version 21 (IBM Corp. Released 2012. Armonk, NY: IBM Corp.). Continuous variables are expressed as the median (range).

Results

The baseline characteristics of the study group are shown in Table 1. Twenty-seven patients were evaluated: 17 were girls, the median age at diagnosis was 0.1 month, and the median body weight was 3.6 kg. Most patients (74.1%) were diagnosed by fetal echocardiography during the antenatal period. Other clinical features at the time of diagnosis were cardiac murmur in one patient, chest pain in one patient, and seizure in two patients. There were 15 rhabdomyomas (55.5%), one fibroma, one angiosarcoma, one rhabdomyosarcoma, and eight unknown tumours, which were suspected of being benign tumours such as rhabdomyomas not associated with tuberous sclerosis. One patient with an unknown type of tumour died on postnatal day 1. All 15 rhabdomyomas were associated with tuberous sclerosis: two were confirmed by histological examination, and 13 were diagnosed clinically as being associated with tuberous sclerosis. Nine of the 15 patients with a rhabdomyoma were confirmed to harbour a tuberous sclerosis complex gene mutation: eight had a mutation in *TSC2* and one a mutation in *TSC1*. Three patients had a small atrial septal defect or small patent ductal arteriosus.

The median follow-up period was 23.0 months. One patient had a family history of cardiac tumours associated with tuberous sclerosis. Seven patients presented in a haemodynamically unstable state. Five patients needed urgent surgery because of a large tumour; two patients had a tumour that caused obstruction of the left ventricular outflow tract, six patients had severe heart failure, and one patient had embolic phenomena.

Histological findings for the tumours were as follows; one angiosarcoma, one fibroma, one rhabdomyosarcoma, and two rhabdomyomas (Table 3). One patient with a rhabdomyoma developed haemodynamically unstable arrhythmia and was treated with antiarrhythmic medication in the acute phase followed by everolimus. One patient with multiple huge tumours died of severe left ventricular dysfunction on postnatal day 1. Excluding the five patients who received an operation, the outcomes of the tumours included 18 with partial regression, two with complete regression, and two with no change. During the follow-up period, for those with partial regression, this occurred at a median of 25.4 months and for the two with complete regression, this occured at a median of 16.1 months; in two patients with no change, this was assessed after a median of 24.2 months.

The echocardiographic features are presented in Table 2. Seventeen patients showed multiple cardiac tumours, and

Table 1 Patient and tumour characteristics

Variable	All tumours
Female, n (%)	17 (62.9)
Age at diagnosis, months, median (range)	0.1 (0-128.5)
Body weight, kg	3.6 (2.3-38.2)
BSA, m^2	0.22 (0.21-1.26)
Symptoms and features at diagnosis, n (%)	Fetal diagnosis 20 (74.1) Cardiac symptoms 2 (7.4) Neurological symptoms 2 (7.4) Incidental diagnosis 3 (11.1)
Tumour type, n (%)	Rhabdomyoma 15 (55.5) Fibroma 1 (3.7) Angiosarcoma 1 (3.7) Rhabdomyosarcoma 1 (3.7) Unknown 9 (33.3)
Follow-up period, months, median (range)	23.0 (3.0-59.8)
Associated anomalies	Tuberous sclerosis 16 Coincidental cardiac lesion 3
Family history	1
Haemodynamically unstable	7
Surgery	5
Death	1
Medication	1
Regression	Partial 18 Complete 2 No change 2

BSA, body surface area.

10 had a single tumour located in the interventricular septum (five patients), right atrium (one patient), mitral valve (one patient), left ventricle (two patients), or right ventricle (one patient). The median cardiac tumour size was 2.0 cm (range, 1.0-6.0 cm). Some patients presented with abnormalities in electrocardiographic recordings, including three with bundle branch block, two with ventricular hypertrophy, four with QT prolongation, four with ST depression, and one with Wolff-Parkinson-White syndrome. Four patients displayed arrhythmias, which involved cardiac arrest, atrial flutter, and premature atrial or ventricular complexes. Table 3 shows the electrocardiographic features by tumour type.

The clinical characteristics and treatment of

Table 2 Echocardiographic and electrocardiographic features

Variable	All tumours
Echocardiographic findings at diagnosis, n	Multiple 17
Largest cardiac tumour size, cm median (range)	2.0 (1.0, 6.0)
Location as a single mass	Interventricular septum 5 Right atrium 1 Mitral valve 1 Left ventricle 2 Right ventricle 1
Symptomatic heart failure, n	6

Table 3 Electrocardiographic features by tumour type

Variable	All tumours	Rhabdomyoma	Fibroma	Angiosarcoma	Rhabdomyosarcoma	Unknown
Patients	27	15	1	1	1	9
Cardiac arrest/VF	1	1	–	–	–	–
Atrial flutter	1	1	–	–	–	–
PAC, PVC	4	4	–	–	–	–
QT prolongation	4	2	–	1	–	1
WPW syndrome	1	–	1	–	–	–
ST depression	4	2	1	–	–	1
LBBB, RBBB	3	1	–	–	–	2
RVH, LVH	2	1	–	–	–	1

Values are expressed as number of patients. VF, ventricular fibrillation; PAC, premature atrial complex; PVC, premature ventricular complex; WPW, Wolff-Parkinson-White; LBBB, left bundle branch block; RBBB, right bundle branch block; RVH, right ventricular hypertrophy; LVH, left ventricular hypertrophy.

Table 4 Haemodynamically unstable patients

Patient	Tumour type	Age at diagnosis (months)	Clinical signs to diagnosis	Haemodynamic unstable symptom	Tumour size and location	Treatment	Outcome
1	Angiosarcoma	128	Chest pain	Massive pericardial effusion	4 cm, right atrium	Surgery	Alive, chemotherapy
2	Fibroma	0	Fetal diagnosis	Hypotension	1.6 cm, right ventricle	Surgery	Alive, right ventricl exclusion, BCPS
3	Rhabdomyosarcoma	94	Seizure	Brain infarction	2.5 cm, mitral valve	Surgery	Alive, chemotherapy
4	Rhabdomyoma	0	Fetal diagnosis	Hypotension	1.4 cm, LVOT	Surgery	Alive
5	Rhabdomyoma	0	Fetal diagnosis	Hypotension	2.4 cm, LVOT	Surgery	Alive
6	Rhabdomyoma	0	Fetal diagnosis	Atrial flutter	4.5 cm, multiple	Everolimus	Alive, complete resolution
7	Unknown	0	Fetal diagnosis	Severe left ventricle dysfunction	4.5 cm, multiple		Death

BCPS, bilateral cavopulmonary shunt; LVOT, left ventricular outflow tract.

haemodynamically unstable patients are listed in Table 4. Patient 1 in Table 4 was diagnosed at 10 years of age and was referred to our clinic for chest pain. Initially, she presented with a huge tumour in the right atrium with massive pericardial effusion. She underwent cardiac surgery for mass excision, was diagnosed with angiosarcoma, and was treated with chemotherapy. She was still alive but in a terminal state at the last follow-up.

Patient 2 was diagnosed in utero. The tumour was a huge single mass in the right ventricle, and the patient exhibited hypotension because the tumour occupied most of the right ventricular cavity. He underwent cardiac surgery. The tumour was determined to be a benign fibroma; however, because the tumour was intramural, we performed only a partial excision. The tumour became larger 2 months later, and the patient was transferred to another hospital where he underwent right ventricular exclusion with a bilateral cavopulmonary shunt at age 7 months. He presented with palpitations, atrial arrhythmia was confirmed, and he was given an anti-arrhythmic agent at the last follow-up.

Patient 3 presented with a seizure caused by embolic phenomena. He had a mitral valve tumour that was confirmed histologically as rhabdomyosarcoma after surgical removal. Patients 1 and 3 with malignant sarcoma chose to be transferred to another hospital for chemotherapy. Patient 3 was not followed up after surgery.

Patients 4 and 5 were diagnosed prenatally with a left ventricular outflow tract tumour. On the first day of life, these patients were managed with prostaglandin infusion to maintain cardiac output. Cardiac surgery with cardiopulmonary bypass was undertaken on postnatal day 2 in these two patients. Rhabdomyomas were confirmed histologically and were associated with tuberous sclerosis. Mutation of *TSC2* was confirmed in both patients. The two patients showed good outcomes and presented with no symptoms and or significant residual tumour at the last follow-up.

Patient 6 was diagnosed antenatally with multiple cardiac tumours but was asymptomatic. Tuberous sclerosis was confirmed in infancy. At age 15 months, he presented with haemodynamically unstable arrhythmia with hypotension and atrial flutter with multiform frequent premature ventricular complexes (Figure 1). The patient was treated initially with direct current cardioversion and was infused with amiodarone and a beta-blocker in the intensive care unit. Because of recurrent arrhythmia, he was treated with everolimus. The patient also exhibited subependymal giant cell astrocytoma in the brain. Five months later, the cardiac tumour had regressed completely after everolimus treatment (Figure 1).

Patient 7 was diagnosed antenatally with multiple huge cardiac tumours mainly in the left ventricle, which were thought to be rhabdomyomas. He died of severe heart failure on postnatal day 1.

The other 20 patients had no significant clinical features or symptoms at the last follow-up.

Discussion

Primary cardiac tumours are rare in infants and children.[5] Most primary cardiac tumours in children are benign, but about 10% are malignant. Even some benign tumours require treatment because of the symptoms.[6] In our patients, most of the cardiac tumours were rhabdomyomas accompanied by tuberous sclerosis and were diagnosed in the antenatal period by fetal echocardiography. This is a similar finding to that in other reports of cardiac tumours in children, but what is unique about our report is that we treated a higher proportion of patients who had been diagnosed in fetal life than in other series.[7,8] Many patients were referred to our centre for a precise diagnosis and further management. Fetal diagnosis did not influence clinical presentation in our analysis. However, fetal diagnosis could be helpful for managing emergent cases that require surgery in the neonatal period. In our centre, fetal echocardiography could detect about 60% of the patients needing surgery; all were managed in the neonatal period and their outcomes were very good. Two patients who had not been diagnosed by fetal echocardiography had malignant tumours, possibly because children with malignant tumours tend to present at an older age than those with benign tumours. Fetal diagnosis is important for determining prognosis and outcome in patients with a haemodynamically compromising tumour.

Most rhabdomyomas took a benign course and needed no treatment, but two patients with rhabdomyomas underwent cardiac surgery because the tumours were located in the left ventricular outflow tract.

Rhabdomyomas usually regress and most require no intervention; therefore, the surgical rate for rhabdomyomas is low compared with other types of cardiac tumours.[6,9] As shown in our study, obstructive rhabdomyoma in the neonate is a critical indication for cardiac surgery. This is one reason for antenatal diagnosis to exclude a high risk of such tumours. One of our patients who presented with haemodynamically unstable arrhythmia had a good response to everolimus, which decreased the tumour size quickly. Everolimus, an inhibitor of mechanistic target of

rapamycin (mTOR), is useful in the treatment of patients with a *TSC* mutation and subependymal giant cell astrocytoma or renal angiomyolipoma. Recent reports have suggested that mTOR inhibitors are also effective in causing regression of previously unchanged cardiac rhabdomyomas.[10,11]

Cardiac surgery is the best option for relieving an outflow tract obstruction. However, surgery might not be as effective as medication in patients with significant arrhythmia caused by multiple cardiac tumours. Extensive intramural myocardial involvement may have a high mortality risk, and patients with such involvement are not considered to be eligible for surgical resection.[11] Our patient also had unchanged multiple cardiac tumours, but everolimus caused marked regression of the tumours, and the patient no longer exhibited arrhythmia. The patient who died had multiple huge cardiac tumours, which were thought to be rhabdomyomas, although we could not confirm the exact tumour type by histological examination.

Although we could not evaluate the risk factors for tumour mortality because of the small sample population, other data have suggested that the risk factors for mortality

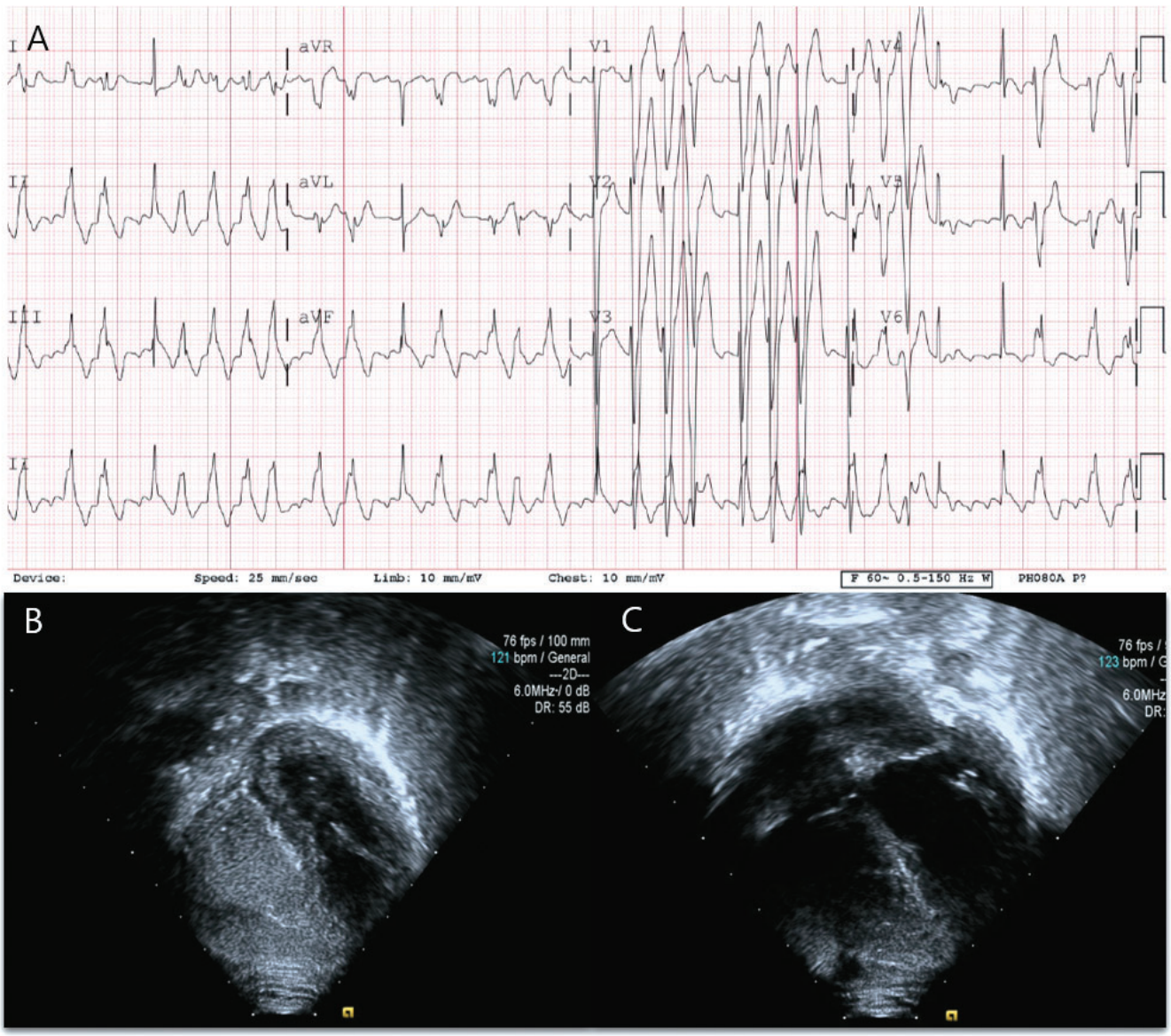

Figure 1 (A) Atrial flutter with multiform frequent premature ventricular complexes in patient 6. (B) Huge mass in the right atrium and ventricle at age 15 months. (C) Regressed tumours after 1 month on everolimus.

are tumour size, dysrhythmia, hydrops, and early age of onset of physiological disturbance.[6] In haemodynamically unstable patients, especially neonates, the primary goals of the treatment are restoration and preservation of sufficient heart function. Continuous intravenous prostaglandin E1 infusion and mechanical ventilator support are important for establishing pulmonary blood flow and haemodynamic stability. The choice of appropriate options for treatment of rhabdomyoma should be made after considering the tumour characteristics.

Of the three other patients who underwent surgery, two had a malignant sarcoma and one had a benign fibroma. Malignant tumours were not diagnosed in the prenatal period but in childhood or adolescence, and were associated with symptoms such as chest pain, which was associated with pericardial effusion, or seizure associated with systemic embolisation of the tumour. Cardiac sarcoma treatment includes primarily excision with curative intent, and these patients were managed with complete resection followed by chemotherapy. However, the results for patients with a malignant tumour are poor; the reported 2-year actuarial survival probability was 14% in a series of 21 patients with primary cardiac sarcomas, and the recurrence of cardiac sarcoma, which is associated with a very poor prognosis, was fairly common.[8,12]

Cardiac fibroma typically presents as a single solid tumour, as in our patients, most commonly in the interventricular septum, but can also be in the wall of any chamber. Fibroma is a benign tumour, but is unencapsulated, invades the myocardium, and averages 5 cm in its largest dimension.[13] Mortality is relatively high in patients with a large infiltrative right-sided fibroma. One of our patients had a large and infiltrative tumour in the right ventricle, but he could not undergo total resection. In the follow-up, the tumour grew at a rapid rate and caused right ventricular dysfunction. The patient underwent right ventricle exclusion with bidirectional cavopulmonary shunt.

The electrocardiographic findings in our study varied, but only one patient died. Cardiac tumours can induce various cardiac arrhythmias, including premature beats, supraventricular tachycardia, ventricular tachycardia, second- or third-degree atrioventricular block, sinus nodal dysfunction, or preexcitation syndrome.[14] Clinically significant arrhythmias were documented in 24% of the patients reported by Miyake's group.[15] They found that the greatest arrhythmia burden occurred in the fibroma patients, who were strongly predisposed to ventricular tachycardia. Arrhythmia control can include medication, placement of an implantable cardioverter defibrillator, or surgical excision. Miyake and colleagues have suggested that tumour resection can be an effective option, especially for patients with ventricular tachycardia. Our rhabdomyoma patients who had atrial flutter with multiple premature ventricular contractions responded to medical management including amiodarone, beta-blocker, and direct current cardioversion. However, frequent relapse of arrhythmia required readmission to the intensive care unit. Although improvement in rhythm status with tumour regression can occur in patients with rhabdomyoma and severe arrhythmia, medical therapy including everolimus may be useful for symptom relief.

Most tumours of unknown origin had a benign course, which appeared as no change, partial regression, or complete regression, except for the one patient who died. Although there was no proven association with tuberous sclerosis, most of them were considered to be benign rhabdomyoma, fibroma, or hamartoma according to the tumour features.

Conclusion

In conclusion, most of the cardiac tumours treated in our centre were rhabdomyomas associated with tuberous sclerosis, although some malignant tumours were found. The surgical outcomes for the cardiac tumours were good. Clinicians should consider various treatment options for haemodynamically unstable paediatric patients with a cardiac tumour.

Declaration of Interest

None

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